UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/608,723	06/26/2003	Andrew R. Marks	19240-594-US1	6915

56949 7590 08/23/2006

WILMER CUTLER PICKERING HALE AND DORR LLP
COLUMBIA UNIVERSITY
399 PARK AVENUE
NEW YORK, NY 10020

EXAMINER	
LI, RUIXIANG	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 08/23/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/608,723	MARKS, ANDREW R.	
	Examiner	Art Unit	
	Ruixiang Li	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-13 and 15-42* is/are pending in the application.

4a) Of the above claim(s) *7-12 and 19-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3-6, 13, 15-18, and 25-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *08/03/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments, and/or Claims

The Request filed on 06/23/2006 for Continued Examination (RCE) under 37 CFR 1.114 of Application 10/608,723 is granted. An action on the RCE follows.

The amendment filed on 06/23/2006 has been entered. Claims 25-42 have been added. Claims 1, 3-13, and 15-42 are pending. Claims 1, 3-6, 13, 15-18, and 25-42 are under consideration.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Withdrawn Objections and/or Rejections

The rejection of claims 1-6 and 13-18 under 35 U.S.C. 102(b) as being anticipated by Nakaya et al. (British Journal of Pharmacology, 131: 1363-1372, 2000), as evidenced by Yano et al. (*Circulation* 107:477-484, 2003), has been withdrawn in view of amended and canceled claims.

Claim Rejections under 35 USC § 112, 1st paragraph

(i). The rejection of claims 4, 5, 16, and 17 under 35 U.S.C.§112, first paragraph for scope of enablement, as set forth at pages 3-5 of the previous office action (Paper No.

04192005, mailed on 04/27/2005), is maintained. New claims 28, 29, 31, and 32 are also rejected on the same basis.

Claims 4, 5, 16, 17, 28, 29, 31, and 32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for treating atrial tachyarrhythmia or inhibiting the onset of atrial tachyarrhythmia in a subject comprising administering to the subject a therapeutically effective amount of an agent that is disclosed in the specification or taught in the art (see below), does not reasonably provide enablement for such a method of employing a genus of agents that inhibits dissociation of FKBP12.6 from RyR2 receptor in a human subject. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with the claims.

The factors that are considered when determining whether a disclosure satisfies enablement requirement include: (i) the quantity of experimentation necessary; (ii) the amount of direction or guidance presented; (iii) the existence of working examples; (iv) the nature of the invention; (v) the state of the prior art; (vi) the relative skill of those in the art; (vii) the predictability or unpredictability of the art; and (viii) the breadth of the claims. *Ex Parte Forman*, 230 USPQ 546 (Bd Pat. App. & Int. 1986); *In re Wands*, 858 F. 2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988).

Claims 4, 5, 28, and 29 are drawn to a method for treating a human subject afflicted with atrial tachyarrhythmia comprising administering to the human subject a therapeutically effective amount of an agent, which inhibits dissociation FKBP12.6 from RyR2 receptor in the human subject's heart, whereas claims 16, 17, 31, and 32 are drawn to a method for inhibiting the onset of atrial tachyarrhythmia in a human subject comprising administering to the human subject a prophylactically effective amount of an agent, which inhibits dissociation of FKBP12.6 from RyR2 receptor in the human subject's heart. Thus, the claims are broad and drawn to a method comprising administration of a genus of structurally undefined agents.

However, the specification merely discloses an agent, JTV-519, and other compounds derived from 1, 4-benzothiazepine (page 28, lines 31-34). The specification fails to provide the characteristic structure that is critical for the function of the claimed genus of agents and fails to provide sufficient guidance and/or working examples on how to make such a genus of agents. The instant specification discloses that methods of screening for compounds to treat heart disease (page 45). However, a method of screening is not equivalent to a method of making an agent that that inhibits PKA phosphorylation of RyR2 receptor or dissociation of FKBP12.6 from RyR2 receptor. While teaching a number of agents that inhibits PKA phosphorylation of RyR2 receptor or dissociation of a FKBP12.6 from RyR2 receptor (Reiken et al., *Circulation* 104:2843-2848, 2001; Doi et al., *Circulation* 105:1374-1379, 2002; Yano et al., *Circulation* 107:477-484, 2003), the prior art does not provide compensatory structural or correlative teachings to enable

one skilled in the art to make the broad genus of agents. In view of the complexity of the nature of the work related to treating heart disease such as atrial tachyarrythmia, it is unpredictable, without a definitive structure, whether a compound has the property of inhibiting PKA phosphorylation of RyR2 receptor or dissociation of a FKBP12.6 from RyR2 receptor. Therefore, it would require undue experimentation for one skilled in the art to make the genus of agents and to use the agents in the claimed methods commensurate in scope with the claims.

(ii). The rejection of claims 4, 5, 16, and 17 under 35 U.S.C.§112, first paragraph for written description, as set forth at pages 5-7 of the previous office action (Paper No. 04192005, mailed on 04/27/2005), is maintained. New claims 28, 29, 31, and 32 are also rejected on the same basis.

Claims 4, 5, 16, 17, 28, 29, 31, and 32 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics,

structure/function correlation, methods of making the claimed product, or any combination thereof.

Claims 4, 5, 28, and 29 are drawn to a method for treating a human subject afflicted with atrial tachyarrhythmia comprising administering to the human subject a therapeutically effective amount of an agent, which inhibits dissociation FKBP12.6 from RyR2 receptor in the human subject's heart, whereas claims 16, 17, 31, and 32 are drawn to a method for inhibiting the onset of atrial tachyarrhythmia in a human subject comprising administering to the human subject a prophylactically effective amount of an agent, which inhibits dissociation of FKBP12.6 from RyR2 receptor in the human subject's heart. Thus, the claims are drawn to a method comprising administration of a genus of structurally undefined agents.

The specification fails to provide any critical structural feature to adequately describe the genus of agents that may be administered in the claimed methods. The specification merely discloses an agent, JTV-519, and other compounds derived from 1, 4-benzothiazepine (page 28, lines 31-34), which are not sufficiently representative of the claimed genus of agents. There is no defined relation between function and structure of the agents in the specification. There is even no identification of any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the agents. Furthermore, although teaching a number of agents

that inhibits PKA phosphorylation of RyR2 receptor or dissociation of a FKBP12.6 from RyR2 receptor (Reiken et al., *Circulation* 104:2843-2848, 2001; Doi et al., *Circulation* 105:1374-1379, 2002; Yano et al., *Circulation* 107:477-484, 2003), the prior art does not provide compensatory structural or correlative teachings to enable one skilled in the art to identify the encompassed compounds as being identical to those instantly claimed. *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of the agents used in the claimed methods, and therefore conception is not achieved until reduction to practice has occurred. Therefore, only the method of administering instantly disclosed and art-taught agents, but not the full breadth of the claims meets the written description provision of 35 U.S.C. §112, first paragraph.

(iii). Response to Applicants' argument

Applicants argue that in view of the amendments presented, the claims are fully described by the subject application and are fully enabled so that one of ordinary skill in the art could carry out the methods claimed without undue experimentation. Applicants submit that the pending claims are directed to methods for treating or inhibiting atrial

tachyarrhythmia in a human subject with an agent, wherein the agent is a derivative of 1,4-benzothiazepine.

This has been fully considered, but is not found to be persuasive because the agents recited in claims 4, 5, 16, 17, 28, 29, 31, and 32 are not limited to 1,4-benzothazepine derivatives.

(iv). Claims 33-36 and 48-81 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for treating atrial tachyarrhythmia or inhibiting the onset of atrial tachyarrhythmia in a human subject comprising administering to the human subject a therapeutically effective amount of JTV-519, does not reasonably provide enablement for such a method of employing a genus of derivatives of 1,4-benzothiazepine. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with the claims.

The factors that are considered when determining whether a disclosure satisfies enablement requirement include: (i) the quantity of experimentation necessary; (ii) the amount of direction or guidance presented; (iii) the existence of working examples; (iv) the nature of the invention; (v) the state of the prior art; (vi) the relative skill of those in the art; (vii) the predictability or unpredictability of the art; and (viii) the breadth of the claims. *Ex Parte Forman*, 230 USPQ 546 (Bd Pat. App. & Int. 1986); *In re Wands*, 858 F. 2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988).

Claims 33-36 are drawn to a method for treating a human subject afflicted with atrial tachyarrhythmia comprising administering to the human subject a therapeutically effective amount of an agent, which enables FKBP12.6 to bind to PKA-phosphorylated type 2 ryanodine receptor (RyR2) channels in the human subject's heart, where the agent is a derivative of 1,4-benzothiazepine, whereas claims and 38-41 are drawn to a method for inhibiting the onset of atrial tachyarrhythmia in a human subject comprising administering to the human subject a prophylactically effective amount of an agent, which enables FKBP12.6 to bind to PKA-phosphorylated type 2 ryanodine receptor (RyR2) channels in the human subject's heart, where the agent is a derivative of 1,4-benzothiazepine. Thus, the claims are drawn to a method comprising administration of a genus of derivative of 1,4-benzothiazepine.

The specification discloses that a single agent, JTV-519, enables FKBP12.6 to bind to PKA-phosphorylated RyR2 (page 93 of the specification). The specification also teaches a number of agents that inhibits PKA phosphorylation of RyR2 receptor or dissociation of a FKBP12.6 from RyR2 receptor (Reiken et al., *Circulation* 104:2843-2848, 2001; Doi et al., *Circulation* 105:1374-1379, 2002; Yano et al., *Circulation* 107:477-484, 2003). However, the specification fails to provide sufficient guidance and working examples on how to make and use other agents that enable FKBP12.6 to bind to PKA-phosphorylated RyR2. The prior art does not provide compensatory structural or correlative teachings to enable one skilled in the art to make the genus of derivative of 1,4-benzothiazepine that enable FKBP12.6 to bind to PKA-phosphorylated RyR2. In

view of the complexity of the nature of the work related to treating heart disease such as atrial tachyarrythmia, it is unpredictable whether a derivative of 1,4-benzothiazepine has the property of enabling FKBP12.6 to bind to PKA-phosphorylated RyR2. Therefore, it would require undue experimentation for one skilled in the art to make and use the claimed invention commensurate in scope with the claims.

Claim Rejections Under 35 U. S. C. § 103 (a)

(i). The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

(ii). Claims 1, 3-6, 13, 15-18, and 25-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nakaya et al. (*British Journal of Pharmacology*, 131: 1363-1372, 2000).

Nakaya et al. teach inhibitory effects of a derivative of 1, 4-benzothiazepine, JTV-519, on experimental atrial fibrillation in Langendorff-perfused guinea-pig hearts. Nakaya et al. teach that perfusion of carbachol (1 uM) shortened monophasic action potential and effective refractory period, and lowered atrial fibrillation threshhold of the guinea-pig hearts. Addition of JTV-519 (1 uM) inhibited the induction of atrial fibrillation by prolonging monophasic action potential and effective refractory period (see, e.g., abstract). Nakaya et al. further that JTV-519 exerts antiarrhythmic effects against atrial

fibrillation and may be useful for the treatment of patients with atrial fibrillation (see, e.g., abstract) or the prevention of atrial fibrillation in patients with ischaemic heart disease (bottom of right column of page 1370). It is also noted that the properties recited in the claims is inherent to the structure of JTV-519.

Nakaya et al. do not explicitly teach treating a human subject. However, it would have been obvious to one having ordinary skill in the art at the time the invention was made to treat a human subject afflicted with atrial tachyarrhythmia by administering to the human subject a therapeutically effective amount of JTV-519 with a reasonable expectation of success. It is a logical and obvious step for one of skill in the art to treat a human subject after a drug is tested successfully in an animal model.

Conclusion

No claims are allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ruixiang Li whose telephone number is (571) 272-0875. The examiner can normally be reached on Monday through Friday from 8:30 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, can be reached on (571) 272-0835. The fax number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, please contact the Electronic Business Center (EBC) at the toll-free phone number 866-217-9197.

Ruixiang Li

Ruixiang Li, Ph.D.
Primary Examiner
August 17, 2006

RUIXIANG LI, PH.D.
PRIMARY EXAMINER